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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
LACOURCIERE, KAREN A

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 01/17/2003

16

Please find below and/or attached an Office communication concerning this application or proceeding.

FILE COPY

Office Action Summary	Application No.	Applicant(s)	
	09/757,100	MONIA ET AL.	
	Examiner	Art Unit	
	Karen A. Lacourciere	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 October 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *45-55* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *45,46 and 48-55* is/are rejected.

7)☒ Claim(s) *47* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

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DETAILED ACTION

Double Patenting

The rejection of record of claims 45-54 under the judicially created doctrine of obviousness-type double patenting over US Patent No. 6,133,031 is withdrawn in response to applicant's amendments filed October 28, 2002.

The rejection of record of claims 45, 46 and 48-54 under the judicially created doctrine of obviousness-type double patenting over co-pending application number 09/615,352 because the scope of the methods claimed in each application no longer encompass the same subject matter.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 45, 46, and 48-55 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for reducing the viability and growth of melanoma tumors using antisense targeted to human focal adhesion kinase of SEQ ID NO:18 inhibiting the viability and growth and invasiveness of melanoma cells treated ex vivo and then administered to the animal, does not reasonably provide enablement for inhibiting tumor cell invasion, using generally any antisense targeted to human focal adhesion kinase, delivered systemically. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The following factors have been considered in formulating this rejection (*In re Wands*, 858F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988)): the breadth of the claims, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, the amount of direction or guidance presented, the presence or absence of working examples of the invention and the quantity of experimentation necessary.

Claims 45, 46 and 48-58 are drawn broadly to methods of treating generally any disease or condition associated with focal adhesion kinase, including generally any type of cancer, using an antisense molecule targeted to focal adhesion kinase or said antisense administered with a chemotherapeutic agent, including 5-fluorouracil.

The specification provides examples wherein cells *in vitro* (cell culture) are treated with antisense targeted to human focal adhesion kinase and the expression of focal adhesion kinase is inhibited, SEQ ID NO:18 is used to inhibit the migration of cells in an in vitro migration assay. The specification provides an example wherein SEQ ID NO:18 inhibits the expression of focal adhesion kinase in melanoma cells *in vitro* (cell culture) and this inhibition is enhanced by coadministration of 5-FU, in vitro. Finally, the specification provides an example wherein SEQ ID NO:18 is administered to xenograft mouse and the growth and metastasis of human melanoma cells is inhibited. The prior art teaches that the growth, viability and invasiveness of melanoma cells can be inhibited when treated with antisense ex vivo, prior to administering the composition comprising the cells and antisense to an animal. The specification does not demonstrate that any other antisense oligonucleotide targeted to focal adhesion kinase (other than SEQ ID NO:18) is capable of inhibiting the growth of melanoma tumors *in vivo* (whole organism) when administered to an animal systemically.

At the time the instant invention was made and even to date, the application of antisense *in vivo* (whole organism) application of antisense without direct evidence is a highly unpredictable endeavor due to target accessibility and delivery issues (see for example Branch, Green et al., Jen et al.). Cell culture examples are generally not predictive of *in vivo* inhibition due to differences in metabolites and clearance rates, local concentration of antisense, and the potential for non-antisense side effects. The field of antisense, to date, does not provide guidelines by which antisense can be routinely targeted to generally any cell type *in vivo* (whole organism) at a concentration effective to result in a treatment effect.

The specification has provided limited guidance for one skilled in the art to practice the invention claimed, however, that guidance would not be sufficient for the skilled artisan to have practiced the claimed treatment methods over the broad scope claimed. One of the major hurdles to the *in vivo* (whole organism) application of antisense is the delivery of an antisense molecule to a target cell at a concentration effective to provide a treatment effect. The examples in the specification which demonstrate treatment effects for neovascularization provide guidance by which a treatment effect is provided when antisense can be delivered locally, by direct injection into the eye, at a high concentration and do not address the instantly claimed methods. The prior art methods of inhibiting melanoma cell viability, growth and invasiveness is also performed ex vivo, and does not provide guidance on systemic delivery. The claimed treatment methods, however, are drawn to delivery of antisense systemically, to generally any tumor cell, including melanoma cells, and inhibiting the growth of the tumor or the viability and invasiveness of the melanoma cells. Further, the specification provides one example of treating a melanoma tumor in a mouse, but the details of

delivery are unspecified, as to whether direct, local administration was used, or if the antisense was delivered systemically.

The specification does not provide specific guidance by which one skilled in the art would expect to be able to deliver antisense targeted to FAK *in vivo* (whole organism) wherein systemic delivery is required, particularly to deliver said antisense at a concentration effective to result in the inhibition of tumor growth, or the reduction of melanoma cell invasiveness or viability. One skilled in the art would not be expected to be able to apply the limited guidance provided by the specification for local administration to generally, nor would one skilled in the art be expected to be able to treat generally any tumor using any FAK targeted antisense based on the example of melanoma tumors using SEQ ID NO:18. Additionally, the prior art methods encompassed in these claims (Cance et al.) is limited to ex vivo methods and would not provide guidance to deliver antisense systemically. Given the unpredictability of antisense methods of treatment *in vivo* (whole organism), it is unclear that the in vitro examples using FAK antisense to inhibit the expression of FAK in adenocarcinoma cells would correlate with the inhibition of the growth of generally any tumor, including melanoma, *in vivo* (whole organism) using any antisense molecule. In order to practice the invention, over the full scope claimed, one skilled in the art would have needed to undergo undue trial and error experimentation, beyond the teachings of the instant specification. How to specifically deliver antisense targeted to FAK *in vivo* (whole organism) systemically to a target tumor cell at a concentration effective to result in inhibition of FAK to a degree required for a treatment effect for a disease or cancer which cannot be treated by local/direct administration of an antisense molecule. Further, it would require that determination of whether or not any other tumor (besides melanoma) can be treated *in vivo* (whole organism) using SEQ ID NO:18 and whether

the *in vitro* (cell culture) inhibition of FAK using other FAK targeted antisense would correlate with a treatment effect *in vivo* (whole organism) for the inhibition of tumor growth, and to reduce the viability and invasiveness of melanoma cells. Additionally, this undue experimentation would include the determination of such factors as dosage, route of administration, disposition of the antisense molecule in tissues, and the half-life and stability of the antisense molecule *in vivo* (whole organism) for the systemic delivery of generally any FAK targeted antisense molecule. Given the art recognized unpredictability of the application of antisense *in vivo* (whole organism) this determination would not be routine, nor would the limited guidance provided for FAK antisense delivered locally be sufficient for one skilled in the art to deliver antisense systemically, to generally any target cell. Although antisense is considered to be a potential therapeutic, there are art-recognized limitations to its applicability *in vivo* (whole organism), particularly problems with delivery, *in vivo* (whole organism) stability, *in vivo* accessibility and toxicity. To overcome the limitations to the *in vivo* (whole organism) application of antisense, one skilled in the art would require specific guidance to predictably apply antisense in the treatment of tumor cell growth, or melanoma cell viability and invasiveness. The specification does not provide this specific guidance for treatment of any disease, or cancer using systemically delivered antisense, or for the treatment of melanoma using any antisense (other than SEQ ID NO:18), nor does the antisense field to date have such general guidelines.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) do not apply to the examination of this application as the application being examined was not (1) filed on or after November 29, 2000, or (2) voluntarily published under 35 U.S.C. 122(b). Therefore, this application is examined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claims 45 and 46 are rejected under 35 U.S.C. 102(e) as being anticipated by Cance et al. (US Patent No. 6,015,893).

Cance et al. discloses a method wherein melanoma cells are treated with FAK antisense of a length of 20 nucleobases and 24 nucleobases long targeted to the coding region of FAK. This composition of antisense and melanoma cells is then injected into an athymic nude mouse and the growth of the cells, the viability of the cells and the tumor cell invasion properties were inhibited. Therefore, Cance et al. anticipates claims 45 and 46.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 45, 46 and 48-54 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cance et al. (US Patent no. 6,015,893) in view of Baracchini et al. (US Patent No. 5,801,154).

Claims 45, 46 and 48-54 are drawn to methods of inhbiting tumor cell invasion, reducing the viability of melanoma cells or inhibiting melanoma cell growth in an animal comprising administering to the animal an antisense compound targeted to focal adhesion kinase. This method would encompass methods wherein the antisense is administered to the animal in a composition with melanoma cells. Additional limitations include wherein the antisense comprises at least one modified internucleoside linkage, including a phosphorothioate, a modified sugar moiety, including a 2'-O-methoxyethyl moiety, a modified base, including a 5-methyl cytosine or wherein the compound is a chimeric oligonucleotide.

Cance et al. teaches a method wherein melanoma cells are treated with FAK antisense of a length of 20 nucleobases and 24 nucleobases long targeted to the coding

region of FAK. This composition of antisense and melanoma cells is then injected into an athymic nude mouse and the growth of the cells, the viability of the cells and the tumor cell invasion properties were inhibited. Cance et al. further teaches that the FAK targeted antisense of their invention can be modified using modified internucleoside linkages, including phosphorothioate (see for example, column 3 and 6), modified using 2'-sugar substituents (see for example, column 7) and by using other modifications to enhance uptake or stability and hybrid formation (see column 7, lines 30-35, for example).

Cance et al. do not actually practice their method using a modified antisense oligonucleotide. Cance et al. do not teach 2'-o-methoxyethyl sugar modifications, modified nucleobases and chimeric oligonucleotides.

Baracchini et al. teach 2'-O-methoxyethyl sugar modifications, 5-methyl cytosine base modifications, chimeric oligonucleotides and modified internucleoside linkages, including phosphorothioate linkages, to increase antisense stability and enhance affinity and antisense oligonucleotides.

It would have been obvious to one of ordinary skill in the art modify the method of inhbiting the growth, invasiveness and viability of melanoma cells taught by Cance et al. by modifying the FAK targeted antisense by incorporating modifications, including 2'-O-methoxyethyl, 5-methyl cytosine, chimeric oligonucleotides and modified internucleoside linkages, including phosphorothioate linkages, as taught by Baracchini et al., because such modifications were routine and well known in the art as modifications which enhance the stability, uptake and affinity of an antisense molecule (see for example

Baracchini et al. column 6, paragraph 3) and because Cance et al. explicitly teaches incorporating modifications into their antisense , including phosphorothioate backbone modifications and 2'-O-sugar modifications and teaches incorporating other art recognized modifications which enhance the uptake, stability and hybridization of an antisense. One of ordinary skill in the art would have been motivated to incorporate the modifications taught by Baracchini et al. into the antisense taught by Cance et al. for the benefits of stability and improved hybridization theses modifications impart. The skilled artisan would have been motivated to incoporate these modifications for use in the claimed methods because these modifications were known to enhance the uptake, stability and hybridization of an antisense in a cell. One of ordinary skill in the art would have expected to be able to practice the methods taught by Cance et al. and using a modified antisense oligonucleotide because the antisense is provided to the cells ex vivo, prior to administration to the animal, which was routine.

Therefore, the invention of claims 45, 46 and 48-54 would have been obvious, as a whole, to one of ordinary skill in the art based on the teachings of Cance et al. (US Patent no. 6,015,893) in view of Baracchini et al. (US Patent No. 5,801,154).

Response to Arguments

Applicant's arguments filed October 28, 2002 have been fully considered but they are not persuasive.

In response to the rejection of record of claims 45-58 under 35 USC 112, first paragraph set forth in the prior Office action (mailed 03-19-02) Applicant argues that

they disagree with the Examiner's suggestion that the references cited in the body of the rejection concerning the unpredictability of antisense technology in vivo is unpredictable. Applicant argues that when these references are read as a whole they teach the potential usefulness of antisense in humans and fail to provide a reasonable basis to doubt that the observed activity for one antisense would not apply to all other antisense targeted to focal adhesion kinase. Applicant argues that Branch, Green et al., Jen et al. and Agrawal et al., do not state that extrapolation from in vitro data or in vivo animal data to in vivo effects in human is unpredictable. Applicant argues that Agrawal et al. admit that many questions concerning the uptake, distribution, side effects and mechanism of action have been answered in recent years. Applicant argues that development of antisense drug products is viewed by skilled artisans as the same as development of any other drug and that the specification provides in vitro cell studies and in vivo animal studies to evaluate dose response relationships and antisense mechanism. Applicant argues that based on the results demonstrated for SEQ ID NO:18 one of ordinary skill in the art would expect that the activity of compounds in cells would be predictive of activity in vivo(whole organism).

These arguments have been considered to the extent that they read on the rejection of claims 45, 46 and 48-55 under 35 USC 112, first paragraph, set forth herein, but have not been found to be persuasive.

The state of the art of antisense for in vivo (whole organism) treatment methods is unpredictable. Read as a whole, the references cited by the examiner in the rejection of record support this conclusion, as pointed out in the rejection of record each of the

references Agrawal et al., Branch, Green et al. and Jen et al. discuss the *potential* for antisense based methods of treatment, however, each of these references conclude that although this potential exists, the state of the art is that therapy methods are not predictable and this is supported by passages from these references cited in the rejection of record. One of the major obstacles to antisense methods in vivo (whole organism) is the specific delivery of an antisense to a target cell. As discussed in the rejection of record, the delivery and uptake of an antisense molecule is unpredictable and variable dependent on a number of factors, including length and sequence composition, etc. Given this unpredictability and variability, the skilled artisan would not expect the delivery of one antisense to correlate generally with the delivery of any antisense in vivo (whole organism).

Claim Objections

Claim 47 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Conclusion

Any rejection of record not repeated herein is considered to be withdrawn.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen A. Lacourciere whose telephone number is (703) 308-7523. The Examiner can normally be reached from 8:30 am to 6:30 pm, Monday-Thursday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader can be reached at (703) 308-0447. The fax phone number for this Group is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Karen A. Lacourciere
1/13/03

KAREN LACOURCIERE
PATENT EXAMINER